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(51) International Patent Classification 6 : <b>A61K 47/48, 48/00, 41/00, C12N 15/62</b>		A3	(11) International Publication Number: <b>WO 95/24928</b> (43) International Publication Date: 21 September 1995 (21.09.95)
(21) International Application Number: PCT/US95/03448 (22) International Filing Date: 15 March 1995 (15.03.95)  (30) Priority Data: 08/213,446 15 March 1994 (15.03.94) US 08/213,447 15 March 1994 (15.03.94) US  (71) Applicant: PRIZM PHARMACEUTICALS, INC. [US/US]; 11035 Roselle Street, San Diego, CA 92121-1204 (US).  (72) Inventors: SOSNOWSKI, Barbara, A.; 1013 Adella Avenue, Coronado, CA 92118 (US). BAIRD, J., Andrew; 5039 Via Papel, San Diego, CA 92118 (US). HOUSTON, L., L.; 327 Pine Needles Drive, Del Mar, CA 92014 (US). NOVA, Michael, P.; 8263 Camino Del Oro #476, San Diego, CA 92037 (US).  (74) Agents: NOTTENBURG, Carol et al.; Seed and Berry, 6300 Columbia Center, 701 Fifth Avenue, Seattle, WA 98104- 7092 (US).		(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).  Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
		(88) Date of publication of the international search report: 12 October 1995 (12.10.95)	
(54) Title: HEPARIN-BINDING GROWTH FACTORS FOR GENE THERAPY AND ANTERIOR EYE DISORDERS			
(57) Abstract			
<p>Preparations of conjugates of a heparin-binding growth factor and a targeted agent and compositions containing such preparations are provided. The conjugates contain a polypeptide that is reactive with an FGF receptor, such as bFGF, or another heparin-binding growth factor coupled to a targeted agent through a linker. The linker is selected to increase the specificity, toxicity, solubility, serum stability, and/or intracellular availability of the targeted moiety. Several linkers may be included in order to take advantage of desired properties of each linker. Pharmaceutical compositions containing these conjugates of FGF and a targeted agent and methods for prevention of recurrence of pterygia, closure of trabeculectomy and corneal haze following excimer laser surgery are provided. The methods entail contacting the area of the eye that has been surgically treated with the composition during or immediately after surgery. Compositions of conjugates of a heparin-binding growth factor and a nucleic acid binding domain are provided. The conjugates bind nucleic acid molecules through the nucleic acid binding domain. These conjugates may be used to deliver nucleic acid encoding a cytotoxic protein or an antisense nucleic acid and the like to cells expressing receptors for the heparin-binding growth factor.</p>			

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## INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 95/03448

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K47/48 A61K48/00 A61K41/00 C12N15/62

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO-A-95 03831 (PRIZM PHARMA INC ;WHITTIER INST FOR DIABETES AND (US)) 9 February 1995 cited in the application see claims ---	1
Y	BIOCONJUGATE CHEMISTRY, vol. 3, 1992 WASHINGTON US, pages 375-381, MICHAEL WESTBY ET AL. 'SEPARATION AND CHARACTERIZATION OF RECOMBINANT PRORICIN CONTAINING AN ALTERNATIVE PROTEASE-SENSITIVE LINKER SEQUENCE.' see the whole document ---	1-4, 7-10, 12, 13, 21, 34, 36, 37, 71, 75 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

1	Date of the actual completion of the international search  10 August 1995	Date of mailing of the international search report  11.09.95
	Name and mailing address of the ISA  European Patent Office, P.B. 5818 Patendaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 cpo nl, Fax (+ 31-70) 340-3016	Authorized officer  Berte, M

## INTERNATIONAL SEARCH REPORT

Internal Application No  
PCT/US 95/03448

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	WO,A,91 18012 (BIOSPAN CORP) 28 November 1991  see page 8, paragraph 2 - page 9, paragraph 2; tables I,II see page 11, paragraph 2; claims see page 10 ---	1-4, 7-10,12, 13,21, 34,36, 37,71,75
A	CHEMICAL ABSTRACTS, vol. 116, no. 15, 13 April 1992 Columbus, Ohio, US; abstract no. 149628, FATTOM, A. ET AL 'Comparative immunogenicity of conjugates composed of the <i>Staphylococcus aureus</i> type 8 capsular polysaccharide bound to carrier proteins by adipic acid dihydrazide or N-succinimidyl-3-(2-pyridyldithio)propionate' cited in the application see abstract & INFECT. IMMUN. (1992), 60(2), 584-9 CODEN: INFIBR; ISSN: 0019-9567, 1992 ---	1-3,9,10
X	WO,A,93 25688 (WHITTIER INST FOR DIABETES AND ;PRIZM PHARMACEUTICALS INC (US); LA) 23 December 1993 cited in the application see page 7, line 22 - line 27 see page 19, line 17 - line 27 see page 34, line 10 - page 35, line 25 ---	1,18-33
A	WO,A,92 04918 (SALK INST FOR BIOLOGICAL STUDI ;ROGER WILLIAMS GENERAL HOSPITAL (US) 2 April 1992 cited in the application see page 6, line 11 - line 34 see page 1, line 16 - line 22 see page 9, line 5 - line 29 ---	38-52
X	WO,A,90 12597 (SALK INST FOR BIOLOGICAL STUDI) 1 November 1990 cited in the application see claims 1-10; example III & US,A,5 191 067 ---	38-52
1		-/-

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 95/03448

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CHEMICAL ABSTRACTS, vol. 111, no. 1, 3 July 1989 Columbus, Ohio, US; abstract no. 1549, DAUCHEL, M. C. ET AL 'Modulation of mitogenic activity and cellular binding of basic fibroblast growth factor by basic proteins' cited in the application see abstract &amp; J. CELL. BIOCHEM. (1989), 39(4), 411-20 CODEN: JCEBD5; ISSN: 0730-2312, 1989</p> <p>-----</p>	53,62,67
1		

**INTERNATIONAL SEARCH REPORT**

In international application No.

PCT/US 95/03448

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:

because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 14-16, 35, 37, 42-52 are directed to a method of treat-

ment of (diagnostic method practised on) the human/animal body the search has  
been carried out and based on the alleged effects of the compositions/compound.

2.  Claims Nos.:

1, 53, 71  
because they relate to parts of the international application that do not comply with the prescribed requirements to such  
an extent that no meaningful international search can be carried out, specifically:

please see enclosure

3.  Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all  
searchable claims.

2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.

3.  As only some of the required additional search fees were timely paid by the applicant, this international search report  
covers only those claims for which fees were paid, specifically claims Nos.:

4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Incomplete Search

2. Obscurities, etc...

In view of the large number of compounds which are designed by the general formulas of claims 1,53,71 the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims or examples (see PCT Search guidelines, Chapter III, paragraph 3.6).

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

Internat'l Application No

PCT/US 95/03448

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9503831	09-02-95	AU-B-	7475694	28-02-95
WO-A-9118012	28-11-91	US-A- CA-A- EP-A- JP-T- US-A-	5169934 2059649 0482185 5502886 5334391	08-12-92 15-11-91 29-04-92 20-05-93 02-08-94
WO-A-9325688	23-12-93	AU-B- CA-A- EP-A-	4635393 2138038 0646174	04-01-94 23-12-93 05-04-95
WO-A-9204918	02-04-92	CA-A- EP-A- JP-T-	2089820 0552188 6501005	20-03-92 28-07-93 27-01-94
WO-A-9012597	01-11-90	US-A- CA-A- DE-D- DE-T- EP-A- JP-T-	5191067 2053275 69010330 69010330 0470183 4507093	02-03-93 28-10-90 04-08-94 20-10-94 12-02-92 10-12-92